DETAILED ACTION

RE: Averback

1. Applicant's response filed on 7/18/2008 is acknowledged. Clams 47-52, and 55-60 are pending. Claims 1-46 and 53-54 have been cancelled. Claims 47, 59 and 60 have been amended.

2. Claims pertaining to the elected species SEQ ID NO: 10 is free of prior art. The search and examination of the claims are extended to the species SEQ ID NOS: 2-9. Claim 52 is rejoined.

3. Claims 47-52, and 55-60 are under examination.

4. It is noted that the "STATEMENT OF COMMON OWNERSHIP" submitted by applicant contains a typographical error. The "WO 02/23915" should be WO 02/34915.

Objections Withdrawn

5. The objection to claim 60 for reciting "a mammal in need a therapeutically effective amount of a neural thread protein (NTP)" is withdrawn in view of applicant's amendment to the claims.

Rejections Withdrawn

6. The rejection of claim 60 under 35 U.S.C. 112, second paragraph for lacking antecedent basis is withdrawn in view of applicant's amendment to the claims.

7. The rejection of claim 60 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of applicant's amendment to the claims.

8. The rejection of claims 47-51, 55-56, and 59-60 under 35 U.S.C. 103(a) as being unpatentable over WO 02/34915A2 (Pub. Date: 5/2/2002, earliest effective filing date: 10/27/2000), in view of Senter (US Patent No.4,874,779, Date of Patent: 10/17/1989), and Xu et al. (US Patent No. 6,620,922B1, Date of Patent 9/16/2003, Filing Date: 8/9/2000) is withdrawn in view of applicant's statement that the instant application and WO 02/34915 were commonly owned or subject to an obligation of assignment to the same entity.

New Grounds of Objection and Rejection

Priority

9. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(3) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the

requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60,273,957, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

The provisional application 60,273,957 does not disclose a method of treating a condition selected from tumor, hyperplasia, hypertrophy, and overgrowth of tissue using the SEQ ID NOs: 2-9. The application 60,273,957 does not disclose sequences of the SEQ ID NOs: 2-9. Accordingly, the claims pertaining to the SEQ ID NOs: 2-9 are not entitled to the date of Application No. 60,273,957.

If applicant believes that support for claims is present in the earliest filed priority document, applicant must, in responding to this action, point out with particularity, where such support may be found.

Claim Rejections - 35 USC § 112, 1st paragraph, 1st paragraph

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 47-52 and 55-59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

This rejection is made because claims 47 and 52 recite the phrase "the proteins identified by SEQ ID NOs: 2-9". The proteins identified by SEQ ID NOs: 2-9 are interpreted to include a genus of proteins which comprise SEQ ID NOs: 2-9, and homologues, variants, and derivatives thereof. The specification teaches that the NTP (including the instant SEQ ID NOs: 2-10) refers to neural thread proteins and related molecules, it also includes biologically active fragments, homologs, variants, derivatives, peptide mimetics, reverse-D peptides, and enantiomers (see page 10, and page 11, lines 10-11). However, the written description in this instant case only sets forth for AD7C-NTP (SEQ ID NO: 10), and the proteins consisting of SEQ ID NOS. 2-9. Therefore the written description is not commensurate in scope with the claim which is

drawn to a method of treating a condition comprising administering to a mammal a genus of proteins including the SEQ ID NOs: 2-10, as well as any homologues, variants, derivatives, mimetics thereof. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016. Although these court findings are drawn to DNA art, the findings are clearly applicable to the claimed proteins.

Vas-cath Inc. 1. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description' inquiry, whatever is now claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See Vas-Cath at page 1116).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Furthermore, although drawn specifically to the DNA art the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly applicable to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus

is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B (1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., F.3d, 2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). Although the instant specification discloses proteins consisting of SEQ ID NOs: 2-10, it fails to provide information about the structures and biological functions of any biologically active fragments, homologs, variants, derivatives, peptide mimetics, reverse-D peptides, and enantiomers of the SEQ ID NOs: 2-10. Therefore, the specification provides neither a representative number of biologically active fragments, homologs, variants, derivatives, peptide mimetics, reverse-D peptides, and enantiomers of the SEQ ID NOS: 2-10, nor does it provide a description of structural and functional features that are common to the fragments, homologs, variants, derivatives, peptide mimetics, reverse-D peptides, and enantiomers of the SEQ ID NOS:. 2-10. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant and encompasses proteins yet to be discovered, the disclosure of the specific species of genus is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide an adequate written description for the inventions as broadly claimed.

Claim Rejections - 35 USC § 112, 1st paragraph

12. Claims 47-52 and 55-59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a condition in a mammal requiring removal or destruction of cells at a site comprising administering to the mammal in need a therapeutic amount of a protein consisting of SEQ ID NO:10, does not reasonably provide enablement for a method of treating a condition in a mammal requiring removal or destruction of cells at a site comprising administering to the mammal in need a therapeutic amount of a protein consisting of SEQ ID NOs:2-9, homologues, variants, or mimetics of SEQ ID NOs: 2-9. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a method of treating a condition in a mammal requiring removal or destruction of cells at a site comprising administering to the mammal in need a therapeutic amount of a NTP, wherein the NTP is administered at the site of the cells

requiring removal or destruction, wherein the condition is selected from the group consisting of a tumor, hyperplasia, hypertrophy, and overgrowth of tissue and wherein the NTP is selected from the group consisting of SEQ ID NO:10 and the proteins identified by SEQ ID NOs:2-9.

The invention is in a class of invention, which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The phrase "proteins identified by SEQ ID NOs: 2-9" is interpreted to include a genus of proteins which comprise SEQ ID NOs: 2-9, biologically active fragments, homologues, variants, derivatives, peptide mimetics, reverse-D peptides, and enantiomers of SEQ ID NOs: 2-9 (see instant specification pages 10-11). Therefore, the claims are drawn to a method of treating tumor, hyperplasia, hypertrophy or overgrowth of tissue by administering to a mammal a genus of proteins including SEQ ID NOs: 2-9, and homologues, derivatives, variants and mimetics thereof.

Quantity of experimentation

The quantity of experimentation in this area is extremely large since there is significant variability in the structure and function of the fragments, homologues, derivatives, variants, and mimetics of SEQ ID NOs: 2-9. Moreover, it would require significant study to determine which of the protein fragments, homologues, derivatives,

variants or mimetics of SEQ ID NOs:2-9 are in fact having same function as SEQ ID NOs: 2-9. The identification and characterization of each of these protein fragments, homologues, derivatives, variants, and mimetics would be inventive, unpredictable, and difficult in itself, requiring years of inventive effort with no guarantee of success in doing so.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to a method of treating unwanted cells using any peptide fragment, homologues, derivatives, variants, and mimetics of SEQ ID NO:2-9 with or without the biological properties representative of what is claimed, and applicant has not even enabled a method of treating such condition using the SEQ ID NOs: 2-9, because it has not been shown that even the SEQ ID NOs: 2-9 are capable of functioning as that which is being disclosed.

The state of the prior art and the predictability or lack thereof in the art:

Regarding the neural thread proteins, de la Monte *et al.* (J. Neuropathol. Exp. Neurol., 1996, 55(10): 1038-1050, IDS) teach that neuronal thread proteins (NTPS) are a family of proteins expressed in brain and neuroectodermal tumor cell lines. De la Monte et al. teach that NTPs are immunologically related to a highly abundant exocrine pancreatic secretory protein known as pancreatic thread protein (PTP), and there are other related molecules overexpressed in hepatocellular and gastrointestinal carcinomas (see page 1038, column 1). de la Monte *et al.* teach that six NTP-immunoreactive molecules (42, 39, 26, 21, 17-18, and 15 kDa) have been detected by

immunoprecipitation, Western blot analysis, or immunoradiometric assay. Each molecule differs in its location and developmental time of expression (page 1038, column 2).

The state of the prior art is different NTPs are expressed in different cells or tissues, such as brain, hepatocellular carcinoma, gastrointestinal carcinoma, and pancreatic juice. Therefore, one skilled in the art would reasonably conclude that these NTPs are likely to have different biological functions. The instant specification does not disclose the functions of the claimed SEQ ID NOs: 2-9.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. It is known in the art that the relationship between the amino acid sequence of a protein (polypeptide) and its tertiary structure (i.e. its binding activity) are not well understood and are not predictable (see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz, et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495). There is no recognition in the art that sequence with identity predicts biological function. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. For example, conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al., J of Cell Bio. 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the

biological activity of the mitogen (Lazar et al. Molecular and Cellular Biology 8:1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p. 1306, col.2). Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to use any of the claimed homologues, derivatives, mimetics and variants of the SEQ ID NOs: 2-9. It cannot be predicted from the disclosure that the SEQ ID NOs: 2-9 would have the same function of the SEQ ID NOs: 10.

Working examples:

The specification teaches an *in vitro* method of treating glioma and neuroblastoma cells by AD7C-NTP (SEQ ID NO. 10), where significant cytotoxic effects

are observed at 24 hrs and at 96 hours after treatment (see page 43, Example 1). The specification teaches a method of administering AD7C-NTP by direct injection to the skin of normal rats, wherein the necrosis is observed in muscle tissue, subcutaneous connective tissue and dermis at the sites where the AD7C-NTP (SEQ ID NO: 10) was injected (see page 45, Example 2). The specification further teaches a method of treating different human and non-human origin tumors by directly infiltrating the tumor with AD7C-NTP (SEQ ID NO: 10), wherein a significant necrosis of tumor cells after AD7C-NTP infiltration is observed (see page 46, Example 3). However, there is no data indicating any of the proteins of SEQ ID NOs: 2-9 has the same effects as the SEQ ID NO: 10. The specification does not teach how to make and use any homologues, derivatives, variants, mimetics of SEQ ID NOs: 2-9. Because the structural features could distinguish the peptide in the genus from others excluded are missing from the disclosure, one skilled in the art cannot envision the detailed structures of the genus. Without such information, one skill in the art cannot practice the claimed invention.

Guidance in the specification

While one of ordinary skill in the art can theoretically produce all of these proteins with art known techniques such as site-directed mutagenesis, given the unpredictability of protein chemistry, it would require undue experimentation to one of ordinary skill in the art to produce all of these different species and thereafter determine their activity. It is art known that certain residues are shown to particularly important to the biological or structural properties of a protein or peptide, e.g., residues in active sites and such

residues may not be generally be exchanged. Skolnick et al teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (Skolnick, et al. Trends in Biotech. 18, 34-39, 2000, see abstract, in particular). Moreover, it is not clear what criteria would be used in deciding which amino acids and how many of them would and could be substituted in SEQ ID NOs: 2-9. Without such guidance, the changes which can be made in the protein structure and still maintain activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016 and Ex parte Forman, 230 USPQ 546 (BPAI 1986). For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Level of skill in the art

The level of the skill in the art is deemed to be high

Conclusion:

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of the art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example to show the effect of SEQ ID NOs: 2-9 balanced only against the high skill level in the art, it is the position of the examiner that it would require undue

experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

14. Claims 47, 49-52, and 55-59 are rejected under 35 U.S.C. 102(e) as being anticipated by Averback et al. (US 7,241,738, Date of Patent 7/10/2007, earliest effective filing date: 11/16/2001).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Averback et al. disclose a method of treating unwanted cellular proliferation such as benign and malignant tumor by administering to a mammal in need a therapeutically effective amount of a NTP peptide (see column 6, last paragraph), wherein the NTP

peptide may be SEQ ID NO: 2 (see Figure 2), and the unwanted cellular proliferation also includes prostatic hyperplasia and tonsillar hypertrophy (see column 51, lines 13-32). Averback et al. teach that the NTP peptides may be employed alone, together, or in combination of other pharmaceutical composition such as cytokines, growth factors, antibiotics etc (see column 52, lines 48-53). The amino acid sequence of SEQ ID NO: 2 is 100% identical to the instant SEQ ID NO: 2 (see sequence alignment Exhibit A).

Conclusion

15. Claim 60 is allowable. Claim 48 is objected to as being dependent on a rejected claim. Claims 47, 49-52 and 55-59 are rejected.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to HONG SANG whose telephone number is (571)272-8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

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Business Center (EBC) at 866-217-9197 (toll-free).

/Hong Sang/
Examiner, Art Unit 1643
10/21/08